CASE REPORT

Discordant courses of COVID-19 in a cohabiting couple of lung transplant recipients

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Abstract

COVID-19 is a novel infectious disease caused by SARS-CoV-2 that emerged in late 2019 and which is now a pandemic. Solid organ transplant recipients are perceived to be at increased risk of severe COVID-19 due to their chronic use of immunosuppressive drugs (ISDs) and to their associated conditions. Scarce data are available on the optimized management of ISDs in these patients and on its impact on presentation, clinical course, viral shedding, and outcome. We report here two cases of COVID-19 in a cohabiting couple of lung transplant recipients for cystic fibrosis, who had different ISDs management and who developed discordant courses of their disease. Our findings suggest that the degree of their immunosuppression might be a reason for their different course and that ISDs might prove partially protective.

KEYWORDS
COVID-19, cystic fibrosis, immunosuppression, lung transplant, SARS-CoV-2, viral pneumonia

1 | INTRODUCTION

COVID-19 is a novel infectious disease caused by the severe acute respiratory distress coronavirus-2 (SARS-CoV-2) that emerged in late 2019 and which is now a pandemic. In a report based on data collected in China from 1099 patients during the first 2 months of COVID-19 outbreaks, 5% of the patients were admitted to the intensive care unit, 2.3% underwent invasive mechanical ventilation, and 1.4% died.[1] Although older patients and patients presenting with coexisting disorders such as hypertension, diabetes, obesity, and renal failure are more prone to suffer from severe disease, data on the impact of COVID-19 in patients with cystic fibrosis (CF), and more particularly in those who have had lung transplant, are scarce.

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A limited report of 40 cases of COVID-19 in CF patients across eight countries, showed that the disease course was similar to that of the general population.[2] In a recent multicenter cohort of 90 solid organ transplant (SOT) recipients (17 with lung transplant), COVID-19 appeared to have more severe outcomes with an overall mortality of 18%.[3] And in a report of 26 kidney-transplant recipients with COVID-19, the patients had less fever at onset but a more rapid clinical progression and a much higher early mortality (28% at 3 weeks) than those in the general population.[4] Another single-center cohort of 28 heart transplant recipients with COVID-19, also reported a high case-fatality rate of 25%.[5]

Regarding immunosuppressive therapy, the general approach in these centers of SOT was to decrease the overall amount of immunosuppression with a particular emphasis on decreasing or stopping antimetabolite drugs such as mycophenolate.[3-5] Of interest, however, are two cases of moderate COVID-19 reported in lung

transplant recipients, who recovered without immune-suppressive drugs (ISDs) modification.[6,7] Currently, it is unclear how immunosuppression impacts on incubation period, presentation of symptoms, viral shedding, and prognoses of COVID-19.

We report here two cases of synchronic COVID-19 in a cohabiting couple of lung transplant recipients for cystic fibrosis but who had discordant courses of their disease. We focus mainly on their ISDs management.

2 | CASES PRESENTATION: A COUPLE OF LUNG TRANSPLANT RECIPIENTS FOR CYSTIC FIBROSIS WITH SYNCHRONIC COVID-19. AN OVERVIEW OF THE TIMELINE IS PRESENTED IN FIGURE 1

2.1 | Case 1

The 40-year-old wife was admitted on March 22 to the emergency room with a 72-hours history of headaches, myalgia, retrosternal burning sensations, and fever. She had no other symptoms and did not report any history of travels abroad nor any exposure to COVID-19 patients, save for her husband with whom she cohabited in a small apartment. She had respected lockdown starting 1 week before French national restrictions were imposed (17th of March) while her husband had continued to work.

The patient had undergone bilateral lung transplantation for cystic fibrosis 19 years earlier and was re-transplanted 13 years later due to chronic lung allograft dysfunction. Her last transplant was then 6 years ago. Her history included insulin-dependent cystic fibrosis-related diabetes (CFRD), hypertension treated with an alpha-blocker (Urapidil), chronic renal failure (baseline serum creatinine of 2.2 mg/dL), and depression treated with a selective serotonin reuptake inhibitor. She had a body mass index (BMI) of 20 kg/m^2, and her ABO blood group type was B. Her maintenance immunosuppressive treatment consisted of tacrolimus (2.5 mg twice per day; trough of 5 µg/mL), mycophenolate (180 mg twice per day; trough of 0.8 µg/mL), and prednisone (5 mg once per day). Her baseline absolute lymphocyte count assessed 2 months prior to developing SARS-CoV-2 infection was of 2.0×10^3/mm^3. There was no history of rejection within the 6 months prior to presentation. Her baseline forced expiratory volume in one second (FEV1) was of 80%.

At admission, she was febrile (38.8°C), eupneic (18 breaths per minute), and with an oxygen saturation of 100% on ambient air. Lung auscultation revealed crackling sounds at both bases.

Biological analysis revealed lymphopenia (1.1×10^3/mm^3), eosinopenia (0.06×10^3/mm^3), an elevated C-reactive protein (CRP) of 33 mg/L. Her liver enzymes, coagulation tests, and D-dimers were all
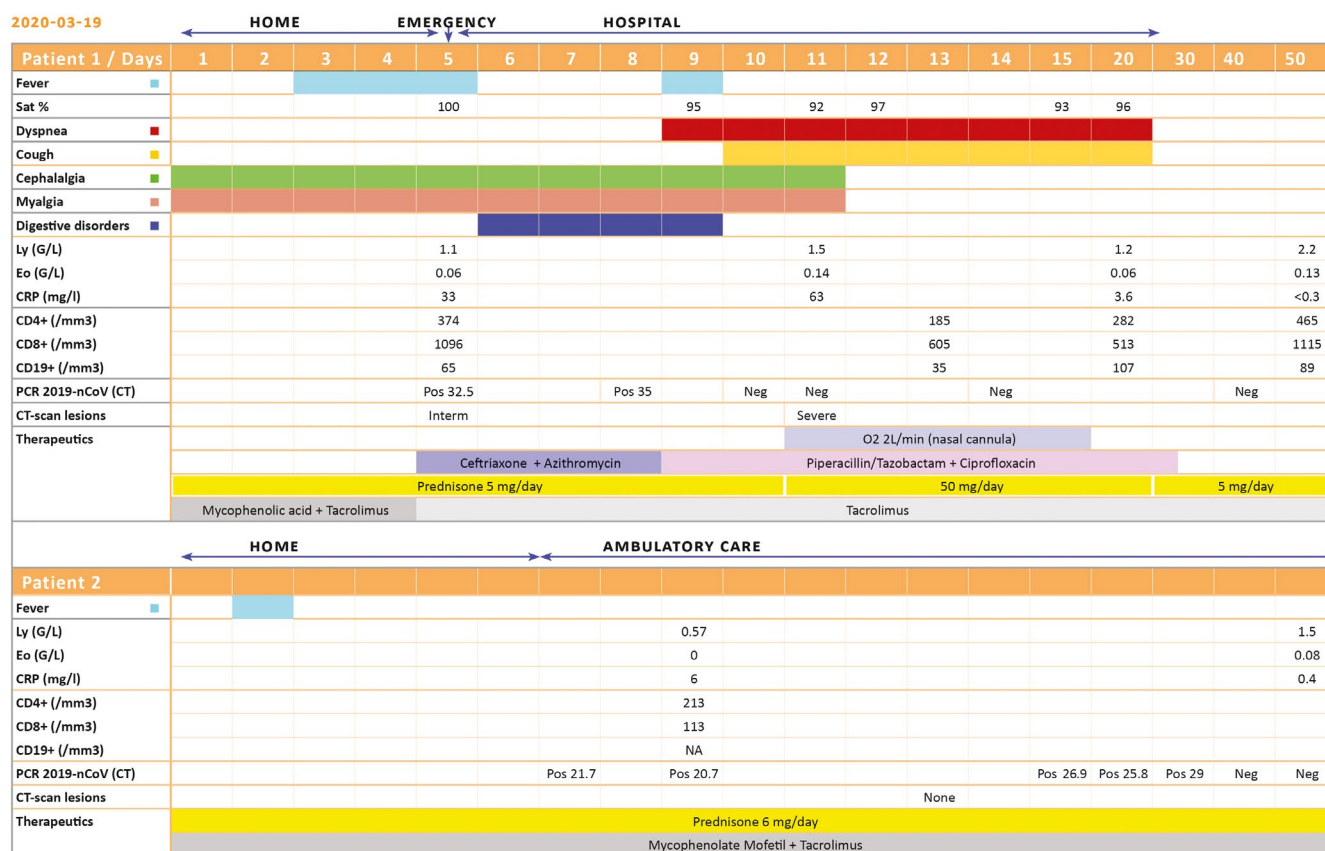

FIGURE 1 Courses of disease and medications. CRP, C-reactive protein; CT, cycle threshold; CT-scan, chest tomography scan; Eo, eosinophiles; Interm, intermediary; Ly, lymphocytes; NA, not available; Sat, oxygen saturation

within normal range. Chest computerized tomography (CT) showed ground-glass opacities in her lung lower lobes and subpleural linear consolidations. Nasopharyngeal swab real-time polymerase chain reaction (RT-PCR) specific for SARS-CoV-2 was positive (32.3 cycle threshold), while tests for other respiratory viruses and bacteria were negative, as well as blood and urine cultures.

At admission, mycophenolate was discontinued, and the patient was started on ceftriaxone (1 g/d) and azithromycin (250 mg/d). Tacrolimus and prednisone were continued at her pre-admission dose (Figure 1).

Six days after onset of her symptoms, she developed nausea, vomiting, diarrhea with worsening kidney function. On Day 9 since symptoms began, her respiratory symptoms got worse, and she developed a productive cough with muco-purulent discharge, dyspnea, and a fever of 39°C. A new chest CT showed a large extension of bilateral ground-glass and linear consolidations primarily located in the lower lung zones, without any adenopathy (Figure 2A). CT angiogram was also completed without any evidence of thrombus.

Her antibiotics were then switched to ciprofloxacin and piperacillin/tazobactam and a nasopharyngeal RT-PCR for SARS-CoV-2 performed the following day (Day 10) was found negative. On Day
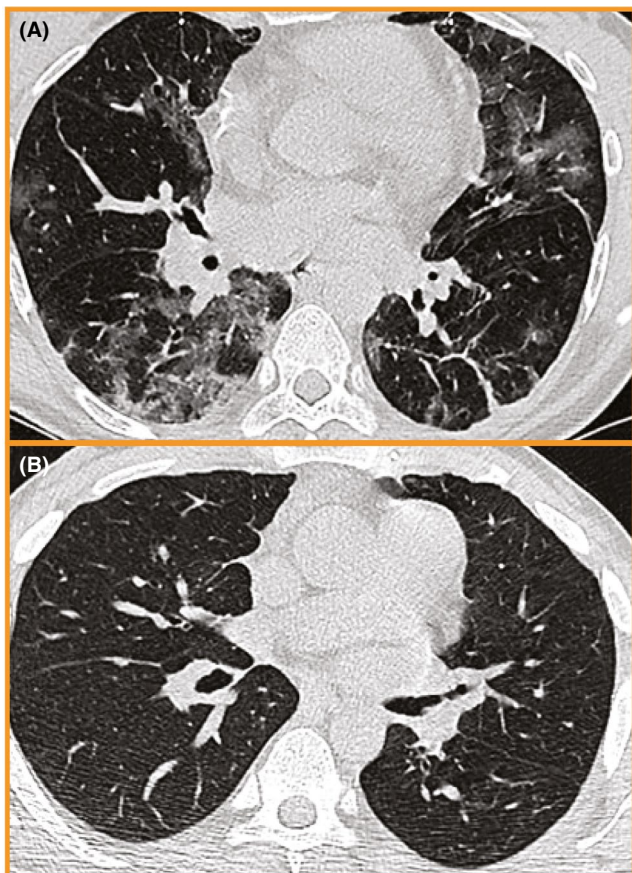

FIGURE 2 Chest computed-tomography scans. A (Patient 1), severe COVID-19 CT-scan showing a "crazy-paving" pattern with ground-glass opacities in the lower lobes and linear consolidations in the subpleural area; B (Patient 2), CT-scan without sign of COVID-19

11 since symptoms began, the patient developed further worsening of her respiratory symptoms accompanied this time with major wheezing and she required oxygen administration of 2 L/min via nasal cannula. She was then given oral prednisolone (1 mg/kg) for 5 days following which her respiratory discomfort improved significantly and her oxygen saturation normalized just on ambient air within 2 days (Figure 1).

The patient was discharged home on Day 20 and did not present any signs of recurrence during a 30-day follow-up. Mycophenolate was restarted 1 month after discharge.

2.2 | Case 2

The 34-year-old husband had undergone bilateral lung transplantation 18 months earlier for cystic fibrosis and had a medical history of chronic renal failure (baseline serum creatinine of 1.9 mg/dL), of insulin-dependent CFRD and of hypertension treated with a calcium channel blocker (amlodipine). He had a BMI of 23 kg/m^2, and his ABO blood group type was O. His maintenance immunosuppressive medications included tacrolimus (7 mg twice a day; trough of 10 µg/mL), mycophenolate mofetil (500 mg twice per day; target dosage of 2.4 µg/mL) and prednisone (6 mg/d). He had no history of rejection within the 6 months prior to presentation. His baseline FEV1 was of 70%.

When his wife was diagnosed with COVID-19 he was tested 2 days later and was found positive for SARS-CoV-2 RNA (CT = 21.7). He then reported high fever for 12 hours 5 days prior to his testing but was otherwise asymptomatic (Figure 1). He did not have any fever or respiratory symptom in the 4 weeks prior to his testing. Biological analysis revealed lymphopenia (0.57×10^3/mm^3) and eosinopenia (0.00×10^3/mm^3), a CRP of 6 mg/L. His absolute lymphocyte counts did not change from his baseline over previous 2 months. His liver enzymes, coagulation tests and D-dimers were all within normal range. The chest CT revealed no lesions without adenopathy nor infiltrates (Figure 2B). Nasopharyngeal RT-PCR testing for SARS-CoV-2 RNA was positive (CT = 21.7). A decision was made to not modify his immunosuppressive maintenance therapy and he remained asymptomatic even though testing repeatedly positive for SARS-CoV-2 for 3 weeks before becoming negative (Figure 1). One month after discharge, his lymphopenia did not resolve completely (absolute lymphocyte count of 0.9×10^3/mm^3).

3 | DISCUSSION

Our report of COVID-19 infection in a couple of lung transplanted recipients demonstrates a different course of the disease in both individuals despite similar comorbidities and environment. Both cohabiting patients were of comparable age, were both afflicted by cystic fibrosis (same genotype) with subsequent lung transplantation, had diabetes, hypertension, and renal failure. In addition, their baseline pulmonary function tests were quite similar, and there was

no history of rejection within the 6 months prior to both presentations. Even though both presented with risk factors for severe COVID-19 disease, their outcome was overall satisfactory. This is in line with several reports of COVID-19 infections in SOT recipients which found prognosis to be similar to that of the general population.[6-9] It is nevertheless different from results from three other cohorts which described a worst outcome.[3-5]

Differences between our two patients included their gender, their antihypertensive treatment, their blood group, and their level of immunosuppression. Studies in China had reported male patients to be more susceptible to severe COVID-19 disease and suffering from a higher mortality rate than females; this however was not the case in our couple patients.[1,10] Despite initial controversies about the role of antihypertensive therapy in the course of the disease, a recent large cohort studies found no substantial increase in the likelihood of being infected or of developing severe infection in relation to the class of antihypertensive medication used.[11] It has been speculated that individuals of blood group type O are less likely to develop severe COVID-19 infection and cardiovascular diseases[12]; this assumption, in line with our case where the husband of blood group type O had developed milder symptoms, has still, however, to be confirmed by large cohort studies.

As for immunosuppression state, our male patient was more severely immunosuppressed than his wife (higher tacrolimus and mycophenolate dosage, no cessation of mycophenolate, lower absolute lymphocyte count, lower CD4$^+$ and CD8$^+$ lymphocytes count), and yet presented with milder symptoms, lesser complications, higher viral load (lower cycle threshold) at the time of presentation, and a prolonged viral shedding without certainty on virus viability.[13] While lymphopenia and lower CD4$^+$ and CD8$^+$ lymphocytes count have been associated with worst outcome and prolonged viral shedding in the general population of COVID-19 patients,[14] other reports suggested that ISDs per se might diminish the "cytokine storm" underlying the development of acute respiratory distress syndrome (ARDS) and subsequent mortality.[15] Of particular interest are recent pathological reports of the presence of overactivated T cells in lung tissue of patients with SARS-CoV-2-induced ARDS.[16] It is therefore possible that patients receiving ISDs such as tacrolimus, mycophenolate or corticosteroids, might be partially protected from this harmful injury, due to the secondary decrease in their number of T cells.

In addition, ISDs have been recently studied for their antiviral properties. Carbajo-Lozoya et al[17] demonstrated that tacrolimus (drug FK506) strongly inhibited the cell culture growth of human coronaviruses SARS-CoV, HCoV-NL63, and HCoV-229E at low, non-cytotoxic, and mycophenolate has been shown to display antiviral activity against MERS-CoV (in vitro and in vivo) and SARS-CoV-1 (in vitro).[18]

The suggested protective role of immunosuppression is also in line with two recent SOT center reports in which ISDs tapering or withdrawal did not halt deterioration of respiratory failure or death, possibly by not blocking immune activation and its secondary harmful cytokine storm.[19,20] In their report of 23 SOT recipients from a single center who were diagnosed with COVID-19, Hoek et al[21] found that the length of hospital stay and mortality were higher in the group of patients in whom the immunosuppression was reduced.

It is also noteworthy that our male patient was recently transplanted (18 months ago) and was characterized by a higher level of immunosuppression, as compared to his wife (re-transplanted 13 years ago). In a recent report from a liver transplant center in Lombardy, Italy, the case-fatality rate related to COVID-19 was 3 out of 111 (2.7%), all three deaths being in long-term transplanted patients on minimal immunosuppressive regimens.[20]

Our brief report is in line with the suggested protective role of advanced ISDs when it comes to transplant recipients with COVID-19. It also argues in favor of the non-modification of the maintenance immunosuppressive therapy in these individuals. Further studies, however, are needed to confirm this role, to optimize the management of ISDs in COVID-19 lung transplant recipients, and to better understand the immuno-pathological mechanisms involved.

CONFLICT OF INTEREST
None to declare.

AUTHOR CONTRIBUTIONS
ND wrote the manuscript and took care of the patients. BC wrote the manuscript and took care of the patients. LA performed the chronogram. CT analyzed the CT scans. MG took care of the patient. MR-G edited the manuscript. PC edited the manuscript and took care of the patient. NC designed the analysis and wrote and edited the manuscript.

INFORMED CONSENT
Informed consent obtained from patients.

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REFERENCES
1. Guan W-J, Ni Z-Y, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382(18):1708-1720.
2. Cosgriff R, Ahern S, Bell SC, et al. A multinational report to characterise SARS-CoV-2 infection in people with cystic fibrosis. *J Cyst Fibros*. 2020;19:355-358.
3. Pereira MR, Mohan S, Cohen DJ, et al. COVID-19 in solid organ transplant recipients: initial report from the US Epicenter. *Am J Transplant*. 2020;20(7):1800-1808.
4. Akalin E, Azzi Y, Bartash R, et al. Covid-19 and kidney transplantation. *N Engl J Med*. 2020;382:2475-2477.
5. Latif F, Farr MA, Clerkin KJ, et al. Characteristics and outcomes of recipients of heart transplant with coronavirus disease 2019. *JAMA Cardiol*. 2020 (Online ahead of print).
6. Aigner C, Dittmer U, Kamler M, Collaud S, Taube C. COVID-19 in a lung transplant recipient. *J Heart Lung Transplant*. 2020;39:610-611.
7. Kates OS, Fisher CE, Stankiewicz-Karita HC, et al. Earliest cases of coronavirus disease 2019 (COVID-19) identified in solid

organ transplant recipients in the United States. *Am J Transplant*. 2020;20:1885-1890.

8. Li F, Cai J, Dong N. First cases of COVID-19 in heart transplantation from China. *J Heart Lung Transplant*. 2020;39(5):496-497.

9. Tschopp J, L'Huillier AG, Mombelli M, et al. First experience of SARS-CoV-2 infections in solid organ transplant recipients in the Swiss Transplant Cohort Study. *Am J Transplant*. 2020 (Online ahead of print).

10. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054-1062.

11. Reynolds HR, Adhikari S, Pulgarin C, et al. Renin-angiotensin-aldosterone system inhibitors and risk of Covid-19. *N Engl J Med*. 2020;382:2441-2448.

12. Dai X. ABO blood group predisposes to COVID-19 severity and cardiovascular diseases. *Eur J Prev Cardiol*. 2020;28:2047487320922370.

13. Wölfel R, Corman VM, Guggemos W, et al. Virological assessment of hospitalized patients with COVID-2019. *Nature*. 2020;581:465-469.

14. Wan S, Yi Q, Fan S, et al. Relationships among lymphocyte subsets, cytokines, and the pulmonary inflammation index in coronavirus (COVID-19) infected patients. *Br J Haematol*. 2020;189(3):428-437.

15. D'Antiga L. Coronaviruses and immunosuppressed patients: the facts during the third epidemic. *Liver Transplant*. 2020;26:832-834.

16. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med*. 2020;8(4):420-422.

17. Carbajo-Lozoya J, Müller MA, Kallies S, Thiel V, Drosten C, von Brunn A. Replication of human coronaviruses SARS-CoV, HCoV-NL63 and HCoV-229E is inhibited by the drug FK506. *Virus Res*. 2012;165(1):112-117.

18. Al Ghamdi M, Alghamdi KM, Ghandoora Y, et al. Treatment outcomes for patients with Middle Eastern Respiratory Syndrome Coronavirus (MERS CoV) infection at a coronavirus referral center in the Kingdom of Saudi Arabia. *BMC Infect Dis*. 2016;16:174.

19. Travi G, Rossotti R, Merli M, et al. Clinical outcome in solid organ transplant recipients with COVID-19: a single-center experience. *Am J Transplant*. 2020.

20. Bhoori S, Rossi RE, Citterio D, Mazzaferro V. COVID-19 in long-term liver transplant patients: preliminary experience from an Italian transplant centre in Lombardy. *Lancet Gastroenterol Hepatol*. 2020;5(6):532-533.

21. Hoek RAS, Manintveld OC, Betjes MGH, et al. Covid-19 in solid organ transplant recipients: a single center experience. *Transpl Int*. 2020.